

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20997**

**ADMINISTRATIVE DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthetic, Critical Care and Addiction Drug Products

MEMORANDUM

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to: Division File, NDA # 20-997

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from: Cynthia McCormick, MD  
Director,  
Division of Anesthetics, Critical Care and Addiction Drug Products

/S/

subject: Chirocaine (levobupivacaine)

sponsor: Parexel

date: February 20, 1999

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This memorandum explicates for the file the basis for the action to be taken on the NDA 20-997 for Chirocaine (levobupivacaine), the pure l-enantiomer of bupivacaine (a product marketed as Marcaine) a local anesthetic agent.

*Background*

Levobupivacaine is a long acting local anesthetic agent and the pure s-enantiomer of bupivacaine approved 1972. Shortly after its approval, bupivacaine was associated with reports of unresuscitatable cardiac arrest due to inadvertent intravascular injection, usually during obstetrical epidural anesthesia. After relabeling bupivacaine to include a Box Warning regarding appropriate use of bupivacaine in obstetrical anesthesia, this problem has largely resolved.

In 1983 after deliberating about the cardiovascular toxicity of bupivacaine the Anesthetics and Life Support Advisory Committee (ALSAC) made a recommendation to the FDA to undertake to assess each new local anesthetic product for very specific actions and mechanisms of action as well as specific mechanisms of toxicity. This resulted in a guidance, which was published approximately two years later which was used as a basis for the current safety development program for this product.

The pure s-enantiomer of bupivacaine, the active ingredient in Chirocaine, was developed as an alternative to bupivacaine as animal studies suggested that it was less cardiotoxic than the currently approved racemic product and therefore would have a superior safety profile with what was hoped would be similar efficacy. The sponsor has suggested specific language in the package insert which distinguishes its purported safety profile from that of bupivacaine, one of which is the Box Warning. The bases for these differences must be understood in terms of the comparative clinical data that are submitted to support them.

### *Efficacy*

Dr. Roberts has done an extensive review of the efficacy of Chirocaine in multiple settings and Dr. Rappaport has provided an excellent summary and secondary review. I concur with their findings.

The effectiveness of levobupivacaine has been demonstrated in controlled clinical trials in the obstetrical setting in studies for C-section using 0.5% levobupivacaine and 0.5% bupivacaine (baseline control assumed) via epidural catheter. The primary measure of efficacy, time to onset of block adequate for surgery (T5 sensory level by pinprick) was achieved. Time to regression of block was also assessed. Similarly efficacy was demonstrated using 0.25% levobupivacaine administered by epidural infusion via catheter in the setting of normal vaginal delivery (labor studies). There were no meaningful differences between levobupivacaine and bupivacaine in terms of efficacy. Fetal outcomes were comparable between the two groups as Dr. Roberts details in the review of safety.

A second group of studies, the Central Block studies, evaluated epidural infusion of levobupivacaine (at concentrations of 0.75% and 0.5%) in lower limb vascular surgery, arthroscopy and major abdominal surgery. These studies were controlled, effectively executed and demonstrated efficacy in duration of block but did not significantly differ from the comparator, bupivacaine.

Controlled pain management studies were performed evaluating levobupivacaine in the postoperative setting. Efficacy was generally based on time to first request for rescue analgesic medication. The studies included studies in postoperative orthopedic surgery, major abdominal surgery.

The final group of studies, the peripheral block studies were performed in a variety of settings included peribulbar, inguinal nerve, and brachial plexus block and local infiltration during dental procedures. These are discussed in detail in Dr. Roberts' review and Rappaport's secondary review of efficacy.

While there is no question that levobupivacaine is an effective local and regional anesthetic agent in for use in a variety of settings as studied, the superiority of levobupivacaine to bupivacaine, or even its equivalence has not been demonstrated. Indeed studies were not really designed for this purpose. While there is sufficient evidence of efficacy to approve this product, there is no basis for any claims of superiority based on efficacy.

### *Safety*

The safety profile of this product derived from prospectively conducted clinical trials in over 1400 patients and subjects has been discussed in the primary review of safety by Dr. Roberts and in my memorandum dated December 29, 1998 provided to the ALSAC. Only the issues that remained at the time of the ALSAC meeting will be summarized in this final action memo.

The relative safety of levobupivacaine compared with bupivacaine has been the subject of two

Advisory Committee Meetings. In review of the ALSAC transcripts from the closed 1997 meeting, there was considerable discussion about what it would take to demonstrate in animals and humans that there is a diminished risk of CNS and cardiovascular toxicities if levobupivacaine is administered by an unintentional intravascular injection, when compared to bupivacaine at the proposed therapeutic doses. The consensus was that at least a 25% difference in specified cardiovascular parameters would be required to satisfy the Committee that the pure enantiomer could be considered safer than the racemate. The review staff and advisory committee evaluated whether this objective was met.

As Dr. Goheer noted in his review of the toxicology of this product there is preclinical evidence derived from a variety of *in vitro* and *in vivo* sources that levobupivacaine has a more favorable cardiovascular profile than bupivacaine, including intracoronary artery infusion in pigs leading to ventricular fibrillation and death in a dose-dependent manner. (The lethal dose was 8 mg versus 5 mg in bupivacaine versus levobupivacaine, respectively). QRS prolongation also occurred at higher doses of levobupivacaine than racemic bupivacaine. In sheep infusion of bupivacaine (150-200 mg) and levobupivacaine (300-350 mg) caused ventricular tachycardia associated with ventricular arrhythmias. Statistical analyses of these differences did demonstrate at least a 25% difference between levobupivacaine and racemic bupivacaine.

There was a fundamental discussion by the Advisory Committee regarding whether the sponsor had established that this apparent advantage is balanced by a similar dose dependent reduction in efficacy, since few studies were done to establish equivalent potency in animal models. In animals, there were two valid *in vivo* rat studies testing the efficacy, and an *in vitro* frog sciatic nerve preparation. (For example, in a study by Gary Strickartz, looking at sciatic nerve block in the rat, he showed that with .1 ml of 0.25% for sciatic nerve block, levobupivacaine and bupivacaine were equipotent on both sensory and motor function.)

Human studies, however, clearly failed to demonstrate any significant advantage of levobupivacaine over bupivacaine both in the infusion studies done in volunteers and in the controlled clinical trials. Its adverse event profile showed similar toxicity to that of bupivacaine. A number of experts on the committee and provided by the Sponsor agreed that the studies submitted represented the maximum ethical attempt to administer this drug to normal volunteers, to examine potential differences in the electrocardiogram. Even though they did not demonstrate any statistically significant changes in the QT interval, most members agreed that it would not be ethical to expose normal volunteers to any more rigorous cardiovascular toxicity studies.

An area of concern is that in the event of an accidental intravascular bolus injection of levobupivacaine, would the ability to resuscitate the patient prove as difficult as it had with bupivacaine. The essential animal data have not yet been completed to assess this. It is generally agreed by both the review staff and the Advisory Committee that the animal studies, which were requested by the previous advisory committee to evaluate the relative ease of resuscitation in the dog model, were essential and should be completed. One advisor suggested that the study should be enriched with more animals as it was in jeopardy of demonstrating ambiguous results due to its small size.

The pharmacologic/toxic effects of levobupivacaine in humans reflects the cardiotoxicity seen with bupivacaine and there is ample documentation in Dr. Roberts' review regarding ECG

changes (QT prolongation), bradycardia, and hypotension that will continue to be reflected in the package insert as it has with bupivacaine. In short, there appears to be no significant difference between the products based on the available clinical data.

To summarize the specific cardiovascular safety evaluation, there are theoretical advantages to levobupivacaine based on preclinical studies, which have not been borne out in the clinical trials. Further information about the relative resuscitability of patients receiving bupivacaine will be expected of the sponsor post approval.

There is a paucity of clinical safety data in the pediatric population. A single pediatric study has been submitted in its completed form to the NDA, and the sponsor has indicated that a number of studies are underway. There is clearly a need for good information in children as young as newborn, and the sponsor will be asked to generate these data.

#### ***Phase 4 Commitments***

The sponsor has committed to the completion of a number of preclinical and clinical studies, most of which are already underway or planned. Agreement to complete these studies was finalized at the time of the Anesthetics and Life Support Advisory Committee. These included

#### **Preclinical Studies to evaluate cardiotoxicity**

1. Direct carotid artery infusion of levobupivacaine with cardiovascular function maintained performed in large mammals (sheep) to evaluate the indirect effect of levobupivacaine on the heart via the CNS.
2. Direct coronary artery infusion of levobupivacaine with CNS function maintained performed in large mammals (sheep) to evaluate the direct effect of levobupivacaine on the heart.
3. Final study report of the cardiovascular resuscitation study in the dog given a convulsive dose of levobupivacaine. This study should be submitted within a maximum of one year following approval.

#### **Preclinical and Clinical Pediatric Studies**

4. Pediatric development program to levobupivacaine in pediatric patients from birth to 16 years of age for anesthesia and pain management. This development plan should include pharmacokinetics and safety primarily, and efficacy data designed to determine appropriate dosing regimens (including continuous infusions).

Finally the sponsor has been asked to consider an additional preclinical study (also requested by the Advisory Committee. The study requested is a developmental toxicity study in a newborn animal model (eg. neonatal pig or newborn beagle).

#### ***Package Insert***

The review of the package insert was conducted by each of the primary reviewers and team leaders and changes were made to the final printed labeling based upon the interpretation of the data from the NDA. This was done in consultation with DDMAC. The most significant issues

relating to the package insert for Chirocaine surround the cardiovascular toxicity—and relate to the need for a box warning as exists for the pure racemate, bupivacaine. This issue has been the subject of discussion at two advisory committee meetings on levobupivacaine and one on ropivacaine, another local anesthetic.

The discussions, deliberations and recommendations of the Anesthetic and Life Support Advisory Committee have been instrumental in guiding the decision about the continued use of a box warning for these products. At the most recent meeting held on January 12, 1999, the following points were made about the current bupivacaine box warning and how it may apply to Chirocaine:

- The box warning is not really relevant to current practice, and doesn't conform to current scientific information.
- The box warning does not focus on the risk of a sudden, large dose of local anesthetic resulting in a toxic blood level.
- The label should reflect the fact that if too much Chirocaine is given resulting in a sudden high blood level, whether with a Biers Block, a block that goes into the jugular vein or carotid artery, with an epidural catheter or a needle that's in vessel, the result could be fatal.
- The box warning that applies to the bupivacaine label states the facts as they were understood at the time—that there had been cardiac arrests and difficult resuscitations and deaths that occurred in patients that had received, presumably large intravascular injections of 0.75% of bupivacaine. It was pointed out that of the original deaths reported in Albright's series, not all the deaths were due to bupivacaine 0.75%, some due to epidacaine as well. None of the 11 was resuscitated by modern standards and in some cases was no anesthesiologist present.
- There are new standards for regional anesthesia practice in obstetrics, and in the main operating room. The practice of anesthesia has standardized such things as giving incremental boluses, and immediate availability of resuscitative equipment, use of multi-orifice catheters.
- Multi-orifice catheters are available now and are being used by most practitioners. (Two recent studies by Norris and colleagues in St. Louis have shown that aspiration of a multi-orifice catheter has a greater than 99.5% chance of reliably detecting intravascular placement just on aspiration.) In 1983, the only catheters available were single orifice catheters.
- Since the bupivacaine warning was added there has been a decrease in the use of epidurals for elective Cesarean Sections, now reserved for only a select group of high risk patients.
- It was suggested that the labeling should bear some warning about the dose-related toxicity of levobupivacaine such as "animal studies demonstrate CNS and cardiac toxicity that is dose-related, thus equal volumes of higher concentration will be more likely to produce toxicity."

- Labeling should reflect the lack of knowledge about fact that the while there may be decreased cardiac toxicity, the resuscitability between this drug and bupivacaine is unknown at this point in time

#### ***Conclusions***

In summary, there is sufficient evidence of the Efficacy and Safety of levobupivacaine for the indications proposed in adults to recommend approval of this application. There is concurrence with the recommendation of the Anesthetics and Life Support Advisory Committee to change the warnings for this product to reflect modern usage. The product will be approved with no box warning, but will continue to warn against the use of 0.75% concentration in the obstetrical setting and provide clear warnings about accidental intravascular injection.

#### ***Action***

NDA 20-997 should be approved for the use of Chirocaine (levobupivacaine hydrochloride) injection in adults for major and minor surgical anesthesia and pain management. The sponsor has requested that the Agency issue an approvable action to allow for further discussion and negotiations of the package insert. There are no other outstanding issues.

APPEARS THIS WAY  
ON ORIGINAL

MAY 29 1998

MEMORANDUM

Date: May 28, 1998

To: Mei-Ling Chen, Ph.D.

Through: John Hunt */S/*

From: Venkata Ramana S. Uppoor, Ph.D. */S/* *05/29/98*

Subject: Filing meeting for NDA 20,997 for Chirocaine™ (levobupivacaine) 2.5, 5.0 and 7.5 mg/ml solution for injection, ~~1S~~-NDA submitted on April 27, 1998 by Parexel Corporation, Waltham, MA (on behalf of Darwin Discovery Limited, Cambridge, England)

Levobupivacaine injection has been developed by the sponsor as a local anesthetic agent. The sponsor proposes to market three dosage strengths, 2.5, 5.0 and 7.5 mg/ml. This is indicated in adults for surgical anesthesia (epidural, intrathecal, peripheral nerve block, local infiltration, oral and ophthalmic surgery) and for pain management; and in children for surgical anesthesia (caudal epidural injection for surgical procedures and post-operative pain) and for pain management. The recommended oral dose depends on the indication and age group. Levobupivacaine appears to have a less potent effect on the cardiovascular system than bupivacaine which may translate to a wider margin of safety as a local anesthetic compared to the racemic bupivacaine.

PHARMACOKINETIC / BIOAVAILABILITY STUDIES

This NDA contains several clinical and pharmacokinetic studies along with literature reports. The formulation used throughout the drug development is same as the to-be marketed formulation. Several studies have been submitted to provide the following data:

1. Mass balance.
2. Single dose pharmacokinetics following IV injection.
3. PK in patients.
4. Comparison of cardiovascular effects following administration of levobupivacaine and racemic bupivacaine.
5. Pharmacokinetic data from several clinical trials conducted in different types of surgery and pain, which utilize all the three strengths (different strengths were used in different studies). These studies compare the pharmacokinetics of levobupivacaine and racemic bupivacaine. Some of these studies also evaluate the pharmacokinetics of R and S-bupivacaine.
6. In vitro metabolism study (metabolized by CYP3A4, 1A2 and 2C9).

7. Protein binding study
8. Assay methodology and validation.

COMMENTS: The following issues have been noted:

1. Several clinical studies have evaluated the pharmacokinetics of S and R-bupivacaine in comparison to racemic bupivacaine. These studies included some dose ranging studies. Hence, dose proportionality in pharmacokinetics of levobupivacaine can be determined. These studies also address the issue of interconversion between R and S-bupivacaine.
2. No pediatric PK data has been submitted. However, clinical studies have been conducted in this patient population.
3. The in vitro protein binding and metabolism study reports have not been submitted in the Human Pharmacokinetics and Bioavailability section. Since this has been submitted under the Pharmacology/toxicology section under volume 1.20, the sponsor should be requested to provide an additional copy of this volume to this reviewer.
4. While PK in both males and females has been studied, no analysis for gender effect has been carried out.
5. Similarly, no data on effects of age, hepatic and renal impairment on PK of levobupivacaine has been provided. This information has also not been mentioned in the proposed package insert. The sponsor should address this issue in the package insert.

RECOMMENDATION: The Human Pharmacokinetics and Bioavailability section of this NDA is organized, indexed, and paginated in a manner to initiate review. Hence, the submission is fileable from OCPB point of view. The sponsor should address the issues identified in comments 3 to 5 above.



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**MEMORANDUM**

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DATE: December 28, 1998

TO: File, NDA 20-997

FROM: Bob A. Rappaport, M.D.  
Deputy Director, DACCADP

THROUGH: Cynthia G. McCormick, M.D.  
Director, DACCADP */s/*

RE: Supervisory Review of Effectiveness for NDA 20-997 Chirocaine  
(Levobupivacaine) injectable

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**BACKGROUND:**

NDA 20-997 for Chirocaine (Levobupivacaine) injectable, was submitted by Darwin Discovery LTD on April 27, 1998. Levobupivacaine is a local anesthetic used for both local and regional anesthesia. Levobupivacaine was developed based on the rationale that the levo- enantiomer would have significantly less cardiotoxicity than the already marketed bupivacaine, which is the racemic mixture of the levo- and dextro- enantiomers. Due to reports of serious cardiac adverse events in obstetrical patients treated with bupivacaine at doses greater than 0.5%, the labeling now contains a black box to warn of potential cardiotoxicity, and specifically contraindicates the use of 0.75% bupivacaine in obstetric patients. In 1996 the sponsor informed the Division that they would be requesting removal of the black box warning for levobupivacaine, then under development. The Division requested an Advisory Committee meeting to discuss the development plan for this product. The Committee was asked to address three questions. These questions and the committee's recommendations follow:

1. What kind and quality of data would be required to remove the box warning from levobupivacaine?

- Safety of levobupivacaine must be demonstrated over several animal models
  - Safety of levobupivacaine must be demonstrated in at least one clinical study that demonstrates at least a 25% increase in safety over bupivacaine, as shown by a shift in the toxicokinetic curve (lidocaine controls were also suggested)
  - Further definition of the nature of the cardiac arrhythmias seen in bupivacaine in a human model
2. Can the committee make any recommendations regarding specific studies, patient populations, or treatment setting that need to be studied to evaluate the risk of the drug in its anticipated clinical usage?
- Initial studies on safety should avoid using patients with history of cardiovascular disease; studies which include cycling females with high progesterone levels would be preliminary to allowing studies for obstetrical use
  - Patients younger than six months should be studied separately from older patients (groups of 2 to 5 years and 6 to 12 years) and a comparison of caudal/epidural continuous infusions is necessary to determine the toxicity levels in children; an open label study, with or without pharmacokinetic subsets, is appropriate for the pediatric population
3. Should levobupivacaine 0.75% be considered for the obstetrical population?
- As the sponsor does not intend to include levobupivacaine 0.75% for use in obstetrics in the NDA, this question was not considered

This application contains twenty-six clinical trials involving 1406 patients. These studies evaluate the efficacy and safety of levobupivacaine injection for use in obstetrics, central and peripheral nerve blocks, epidural and infiltrative postoperative pain management, and pediatric patients. In addition, there are seven ongoing studies, an anesthetic "special analysis" conducted on cardiac measures evaluated in two studies, and two studies which were not integrated into the database as they were not available at the time the database was locked.

The clinical studies of the effectiveness and safety of this new product have been reviewed by Monica Roberts, M.D. The application has also been reviewed by Yi Tsong, Ph.D. (biostatistics), Suresh Doddapaneni, Ph.D. (clinical pharmacology and biopharmaceutics), Anwar Goheer, Ph.D. (pharmacology/toxicology), and Pramoda Maturu, Ph.D. (chemistry). Thomas Permutt, Ph.D. has contributed a supervisory biostatistics review. Cynthia McCormick, M.D., Division Director, will be contributing a supervisory review of clinical safety. In this memo, I will briefly review the effectiveness data summarized in the primary clinical review, as well as any relevant information found in the primary reviews from the other disciplines, and make appropriate recommendations for action on the NDA.

## **EFFECTIVENESS:**

Evidence of efficacy has been submitted in 17 clinical trials. Two trials (030632 and CS-001) evaluated 0.5% levobupivacaine compared to 0.5% bupivacaine for epidural anesthesia during cesarean section. Two trials (030276 and 030433) evaluated levobupivacaine compared to bupivacaine (at various doses) for epidural anesthesia during labor. Two trials (006175 and CS-005) evaluated levobupivacaine compared to bupivacaine (0.5% and 0.75% doses) for epidural block for lower limb orthopedic and abdominal surgery. Four studies (030475, CS-004, CS-006 and 030742) evaluated levobupivacaine alone at various concentrations or with morphine, with fentanyl and with clonidine for epidural block for post-operative pain management. Six studies (030428, 030721, 006154, 030543, 030737 and 030700) evaluated levobupivacaine for peripheral nerve block or post-operative pain control by infiltration: two studied infiltration for post-inguinal hernia repair in adults; one studied brachial plexus block for hand surgery; two studied peribulbar block for eye surgery; and one studied infiltration for post-operative dental pain control. In most cases these studies compared levobupivacaine to bupivacaine in equivalent or varying doses. The dental study compared levobupivacaine to lidocaine with epinephrine and to placebo. Study CS-007 evaluated levobupivacaine compared to no treatment for ilioinguinal-iliohypogastric nerve block in pediatric patients undergoing herniorrhaphy.

## **CESAREAN SECTION STUDIES:**

### **Study #030632:**

This was a randomized, double-blind, parallel group study comparing 0.5% levobupivacaine to 0.5% bupivacaine for epidural anesthesia in patients undergoing elective cesarean section. The study was performed at two centers.

Patients were randomized to one of the two treatment arms, either 0.5% levobupivacaine or 0.5% bupivacaine via epidural catheter, just prior to elective cesarean section. Twenty five milliliters of study drug was infused over 15 minutes. If, at 30 minutes from the start of the infusion, adequate block was not achieved, an additional 5 mL was infused over 5 minutes. If an adequate block was not achieved after administration of the maximum dose, the patient was withdrawn from the study. The maximum dose was changed by amendment on January 27, 1997. This amendment allowed for the administration of an additional 10 mL dose of study drug if the duration of surgery required additional block.

The primary measure of efficacy was the time to onset of block adequate for surgery, which was defined as the time from completion of drug administration until a sensory level (by pinprick) of T5 bilaterally, or one side at T4 with the other at T6, was achieved. Block level was recorded at 0, 2, 5, 10, 15, 20, 25, 30, 45 and 60 minutes, or until the T4

to T6 level was achieved. The block level was then assessed every 30 minutes until it had regressed to the T10 level; after which it was assessed hourly until full recovery.

Secondary efficacy measures included:

- 1) Time to onset of "clinically adequate (not necessarily T5 bilaterally) block;
- 2) Time to onset of any sensory block (in any dermatome);
- 3) Time to sensory block offset (all dermatomes);
- 4) Proportion of patients with any motor block prior to surgery;
- 5) Proportion of patients responding at each grade of motor block;
- 6) Time to offset of motor block (recovery of full movement);
- 7) Average quality of analgesia;
- 8) Muscle relaxation as assessed by anesthetist and obstetrician (5 point scale);
- 9) Overall assessment of block by anesthetist and obstetrician (3 point scale);
- 10) Proportion of patients requiring extra 10 mL of study drug.

#### Results:

Of the 69 patients randomized, 67 received study medication and were included in the safety analysis. Of the remaining 67 patients, 3 were excluded from the Intent-to-Treat [ITT] population because block was not achieved due to technical failure. Another 2 patients were excluded from the Per-Protocol [PP] population due to having received prohibited pre-dose medication. Finally, the sponsor also dropped a further 5 patients from their analysis on the basis of "inadequate block."

The following table, copied from Dr. Roberts' Table 2, page 21 of her review, summarizes patient disposition for this study:

Table 1.

PATIENT NUMBER	0.5% LEVOBUPIVACAINE N (%)	0.5% BUPIVACAINE N (%)	PATIENT TOTALS N (%)
Randomized	35	34	69 (100)
Excluded from Safety Population	2	0	2
Safety Evaluable	33 (94.2)	34 (100)	67 (97.1)
Excluded from Intent-to-Treat:	2	1	3
Intent-to-Treat Population	31 (88.6)	33 (97)	64 (92.7)
Excluded from Per- Protocol:	0	2	2
Per-protocol Population	31 (88.6)	31 (91.2)	62 (89.8)
Excluded from Evaluable Primary Efficacy Patients:	2	3	5
Evaluable Primary Efficacy Patients:	29 (83)	28 (82.3)	57 (82.6)
5 (0.07%) Total Discontinued from Study			64 (92.7%) Total Completed

An unspecified number of patients at one center (001) received a second epidural injection of study drug even though they had already achieved an adequate block. Another unspecified number of patients at a second center (002), who did not achieve adequate block at 15 minutes, did not receive a second dose of study medication as called for in the protocol. The significance of these protocol errors is unclear. The statistical reviewer for this application, Dr. Tsong, found these numbers to be a potential source of bias, but without a clear direction.

All patients who did not achieve a "per-protocol adequate block" were treated at Center 002. However, there was not a statistically significant difference between the levobupivacaine and bupivacaine treated patients who did not achieve adequate block at this center. There was a generally longer time to onset of block for the patients at Center 002 compared to Center 001.

Treatment groups appeared to be generally matched on relevant measures at baseline.

***Primary Efficacy Analyses:***

The mean times to onset of protocol adequate block in the ITT population were 10.2 minutes and 9.0 minutes, for levobupivacaine and bupivacaine, respectively. The treatment-difference was 1.6 minutes with 95% confidence intervals [CI] of (-2.01, 5.21). These were within the  $\pm 10$  minutes "equivalence limit" defined by the sponsor.

***Secondary Efficacy Measures:***

All secondary efficacy results are based on analyses performed on the PP population.

**Time to Onset of Clinically Adequate Block:**

The mean times to onset of clinically adequate block were 12.6 and 11.4 minutes for levobupivacaine and bupivacaine, respectively. The treatment difference was 1.5 minutes with 95% CI of (-1.69, 4.69).

**Time to Onset of Any Sensory Block:**

The mean times to onset of any sensory block were well balanced between the groups [see Dr. Robert's Table 10, page 27 of her review] and there was no statistically significant difference ( $p = 0.65$ ). The onset of any sensory block occurred immediately upon completion (time zero) of the epidural in 87% of patients in each treatment group.

**Time to Sensory Block Offset:**

The mean times to offset of sensory block were 485.9 minutes and 462.7 minutes for levobupivacaine and bupivacaine, respectively. The treatment difference was 19.0 with 95% CI of (-53.2, 91.2). This failed the equivalence criterion stated in the protocol.

**Proportion of Patients with Any Motor Block Prior to Surgery:**

Forty-two percent of levobupivacaine patients and 26% of bupivacaine patients recorded no motor block prior to surgery. The odds ratio of having recorded motor block was 2.03 with 95% CI of (0.66, 6.23). The difference in percentage was not statistically significant ( $p = 0.22$ ).

**Proportion of Patients Responding at Each Grade of Motor Block:**

Patients in the levobupivacaine group reported lower grade motor block more frequently than patients in the bupivacaine group: 29% vs. 10% in grade 0, 48% vs. 48% in grade 1, 13% vs. 26% in grade 2, and 10% vs. 16% in grade 3, for levobupivacaine and bupivacaine, respectively. There was a statistically significant difference with  $p = 0.037$ .

### Time to Offset of Motor Block:

The mean times to offset of motor block were 241.9 minutes and 171.8 minutes, for levobupivacaine and bupivacaine, respectively. The treatment difference was 48.0 with 95% CI of (10.0, 90.0).

### Average Quality of Analgesia:

Using a 100 mm Visual Analogue Pain scale, measurements were made at skin incision, abdominal opening, uterine incision and in the recovery room. The parameter for comparison was defined as the mean of the four measures. The mean (median) was 8.23 (2.33) mm and 4.46 (0.25) mm for levobupivacaine and bupivacaine, respectively. The treatment difference was estimated as 0 (2.08) mm with 90% CI of (0, 2.5) [95% CI of (-0.21, 4.52)].

### Muscle Relaxation:

Using a 5 point rating scale (0 = worst; 4 = best), the results of the anesthesiologists' assessments were: 6% vs. 10% rated fair, 87% vs. 71 % rated good, and 6% vs. 19% rated best, for levobupivacaine vs. bupivacaine, respectively. The results of the obstetricians' assessments were: 3% vs. 0% rated poor, 3% vs. 13% rated fair, 87% vs. 74% rated good, and 6% vs. 13% rated best, for levobupivacaine vs. bupivacaine, respectively. The differences were not statistically significant ( $p = 0.46$  and  $0.96$  for the anesthesiologists and obstetricians, respectively).

### Overall Assessment of Block:

Using a 3 point scale (0 = failure, 1 = unsatisfactory block, and 2 = satisfactory block) the anesthesiologists and obstetricians each rated the block for overall quality. There were no statistically significant differences between the two treatment groups in either the anesthesiologists' (55% levobupivacaine patients vs. 77% bupivacaine patients rated satisfactory) or the obstetricians' (87% vs. 90%) assessments ( $p = 0.069$  and  $0.69$  for the anesthesiologists and obstetricians, respectively).

### Proportion of Patients Receiving Extra 5 mL Study Drug:

Although the amended protocol called for an analysis of the proportion of patients who received an extra 10 mL of study drug during surgery, the sponsor has analyzed the proportion of patients who received an extra 5 mL of study drug. Ten percent of levobupivacaine patients received an additional 5 mL compared with 3% of bupivacaine patients. The difference was not statistically significant.

**Comments:**

The sponsor has provided evidence that 0.5% levobupivacaine and 0.5% bupivacaine are equivalent for use as an anesthetic during cesarean section. The measure used to define this attribute was time to onset of protocol adequate block. Thirty of 32 patients on levobupivacaine and 29/32 patients on bupivacaine achieved adequate block for cesarean section. While the levobupivacaine was clearly effective as an anesthetic, as per Dr. Permutt's supervisory statistical review, the equivalence criteria ( $\pm 10$  minutes) defined by the sponsor make little sense in the face of the averages for the two study groups, which were each within one minute of ten minutes. In addition, as per Dr. Roberts' comments, the longer time to offset of motor block for levobupivacaine compared to bupivacaine is of some clinical concern.

**Study CS-001:**

This was a randomized, double-blind, parallel group study comparing 0.5% levobupivacaine to 0.5% bupivacaine for epidural anesthesia in patients undergoing elective cesarean section. The study was performed at a single center.

Patients were randomized to one of the two treatment arms, either 0.5% levobupivacaine or 0.5% bupivacaine via epidural catheter, just prior to elective cesarean section. Thirty milliliters of study drug was infused over 15 to 20 minutes. If an adequate block was not achieved after administration of the maximum dose, the patient was withdrawn from the study.

The primary measure of efficacy was the time to onset of block adequate for surgery, which was defined as the time from completion of drug administration until a sensory level (by pinprick) of T5 bilaterally, or one side at T4 with the other at T6, was achieved. Block level was recorded at 0, 2, 5, 10, 15, 20, 25, 30, 45 and 60 minutes, or until the T4 to T6 level was achieved. The block level was then assessed every 30 minutes until it had regressed to the T10 level; after which it was assessed hourly until full recovery.

Secondary efficacy measures included:

1. Time to sensory block offset;
2. Time to onset of motor block;
3. Time to offset of motor block;
4. Time to onset of anesthesia;
5. Quality of anesthesia (by 100 point pain scale);
6. Muscle relaxation as assessed by anesthetist and obstetrician (5 point scale);
7. Overall assessment of block by anesthetist and obstetrician (3 point scale);

## Results:

Of the 65 patients randomized, 63 received study medication and were included in the safety analysis. Of the remaining 63 patients, 1 patient in the bupivacaine group experienced an intravascular injection and was discontinued from the study. She did not have a post-treatment efficacy evaluation and was, therefore, not included in the ITT analysis. Another 2 patients (both in the levobupivacaine group) were excluded from the PP population due to treatment failure requiring additional medication above the allowed 30 mL. Thirty patients were included in each arm of the PP population.

Treatment groups appeared to be generally matched on relevant measures at baseline.

### *Primary Efficacy Analyses:*

The mean times to onset of protocol adequate block in the ITT population were 9.8 minutes and 6.4 minutes, for levobupivacaine and bupivacaine, respectively. The difference was statistically significant with  $p = 0.023$ . The mean difference was 3.5 minutes with 95% CI of (0.2, 6.7). The CI limits lie within the pre-specified equivalence limit. However, Dr. Roberts notes, on page 53 of her review, that, "...an equivalence limit of  $\pm 7.26$ , which is  $>100\%$  of the mean onset time of bupivacaine, ... allows levobupivacaine to take twice as long as bupivacaine to onset of sensory block and still be judged equivalent."

### *Secondary Efficacy Measures:*

All secondary efficacy analyses were performed on the ITT population, unless otherwise specified.

#### Time to Offset of Sensory Block:

The mean times to regression of block to T10 were 392.2 minutes and 317.1 minutes for levobupivacaine and bupivacaine, respectively. The mean difference was 12.1 minutes with 95% CI of (-29.1, 53.3). The difference was not statistically significant with  $p = 0.559$ . The mean times to complete offset of sensory block were 451.0 minutes and 428.1 minutes for levobupivacaine and bupivacaine, respectively. The mean difference was 22.9 minutes, with 95% CI of (-12.7, 58.5). The difference was not statistically significant with  $p = 0.257$ .

#### Time to Onset of Motor Block:

Motor block occurred in 81.3% of patients in the levobupivacaine group and 93.3% of patients in the bupivacaine group. The mean times to onset of motor block were 17.2

minutes and 12.5 minutes for levobupivacaine and bupivacaine, respectively. The mean difference was 4.7 minutes, with 95% CI of (-0.6,10.0). The difference was not statistically significant with  $p = 0.075$ .

#### Time to Offset of Motor Block:

The mean times to offset of motor block were 241.2 minutes and 265.2 minutes for levobupivacaine and bupivacaine, respectively. The mean difference was 24.0 minutes with 95% CI of (-68.3, 20.3). This difference was not statistically significant with  $p = 0.446$ . The sponsor also analyzed degree of motor block at various time points during the presurgical and surgical periods. The comparisons between the two treatment groups showed occasional differences which were statistically significant for one side or the other in a clinically irrelevant pattern.

#### Time to Onset of Anesthesia:

The mean time to onset of anesthesia was 0.5 minutes for both the levobupivacaine and the bupivacaine treatment groups, with 95% CI of (-0.9, 0.8). There was no statistically significant difference between the groups with  $p = 0.942$ .

#### Quality of Anesthesia:

Patients assessed their level of pain on a scale of 1 = no pain to 100 = very painful, at five points during surgery, post-delivery, and in the recovery room. The parameter for comparison was defined as the mean of the five measures. The means were 0.64 and 1.65 mm for levobupivacaine and bupivacaine, respectively. The difference was -1.0 with 95% CI of (-3.1, 1.0). There was no statistically significant difference between the two treatments at any single event.

#### Muscle Relaxation:

Using a 5 point rating scale (0 = worst; 4 = best), the results of the anesthesiologists' assessments revealed mean scores of 3.8 for the levobupivacaine group and 4.0 for the bupivacaine group. The mean difference was -0.2 with 95% CI of (-0.3,0.3). The difference was statistically significant with  $p = 0.052$ . The results of the obstetricians' assessments revealed mean scores of 3.8 for the levobupivacaine group and 3.7 for the bupivacaine group. The mean difference was 0.1 with 95% CI of (-0.3,0.3). The difference was not statistically significant with  $p = 0.583$ .

#### Overall Assessment of Block:

Using a 3 point scale (0 = failure, 1 = unsatisfactory block, and 2 = satisfactory block, the results of the anesthesiologists' assessments revealed mean scores of 2.0 for the levobupivacaine group and 2.0 for the bupivacaine group. The results of the obstetricians' assessments also revealed mean scores of 2.0 for the levobupivacaine group and 2.0 for

the bupivacaine group. There were no statistically significant differences for either assessment.

#### **Comments:**

The sponsor has provided evidence that 0.5% levobupivacaine and 0.5% bupivacaine are equivalent for use as an analgesic during cesarean section. The measure used to define this attribute was time to onset of protocol adequate block. Thirty of 32 patients on levobupivacaine and all 32 patients on bupivacaine achieved adequate block for cesarean section. However, levobupivacaine had a statistically significantly longer time to onset of sensory block adequate for cesarean section. While the levobupivacaine was clearly effective as an anesthetic, as noted by Dr. Permutt in his supervisory review, the equivalence criterion (a difference of no more than 7.6 minutes) defined by the sponsor makes little sense in the face of the averages for the two study groups which were 10 minutes for levobupivacaine and 6 minutes for bupivacaine. In this study, although not statistically significant, the mean time to offset of motor block was longer for bupivacaine compared with levobupivacaine.

#### **LABOR STUDIES:**

##### **Study 030276:**

This was a randomized, double-blind, parallel group, multicenter study comparing 0.25% levobupivacaine to 0.25% bupivacaine for epidural anesthesia in patients in labor.

Patients were randomized, with stratification by primigravida vs. multigravida, to one of the two treatment arms, either 0.25% levobupivacaine or 0.25% bupivacaine, via epidural catheter. Ten milliliters of study drug was infused (initially 3 mL at 1 mL/2 sec. as test dose, followed after 5 minutes by 7 mL at 1 mL/2 sec.) and followed by further 10 mL 'top-up' doses (at 1 mL/2 sec.) as needed, with a minimal interval between doses of 15 minutes. The maximum number of 'top-up' doses was 8 (changed by protocol dated 5/15/96 to 7) and the total dose of study drug allowed in a 4 hour period was 2 mg/kg.

The primary measure of efficacy was the duration of pain relief, defined for the ITT population as the time from the first painless contraction until the next 'top-up' injection. For the PP population, the duration of pain relief was defined as the time from the first painless contraction until the time of the second successive painful contraction, whether or not a 'top-up' dose was administered during that period. Patients completed a verbal rating scale (0 = painful; 1 = aware but not painful; 2 = unaware) for 2 contractions before the epidural and, thereafter, at every contraction until the first 'top-up' dose was administered. After the first 'top-up' dose, they rated their pain level at every contraction until the second 'top-up' dose. Recordings were then made every 30 minutes until the next 'top-up' dose, and immediately prior to each subsequent 'top-up' dose. For ITT

patients who received a 'top-up' dose before experiencing their second painful contraction, the duration of pain relief was to be calculated from the time of first painless contraction until the time of 'top-up' dosing. This was under the assumption that the decision to give the 'top-up' dose was made because of inadequate pain relief.

Secondary efficacy measures included:

1. Duration of pain relief following each 'top-up';
2. Time to pain relief following each dose of study drug;
3. Time normalized area under the Visual Analogue Scale (VAS) pain score vs. time cure (AUC) for all assessments following each dose of study drug using the linear trapezoidal rule;
4. Proportion of patients recording each grade of motor block;
5. Sensory block;
6. Overall quality of analgesia.

#### Results:

Of the 169 patients randomized, all 169 received study medication and were included in the safety analysis. Of these 169 patients, 7 were considered technical failures and were not included in the ITT analysis. Another 25 patients (8 in the levobupivacaine group; 17 in the bupivacaine group) were excluded from the PP population due to various protocol violations. A total of 137 patients (68 levobupivacaine; 69 bupivacaine) were included in the PP population. Of these 137 patients, 30 (20 levobupivacaine; 10 bupivacaine) did not achieve pain relief and were not included in the analysis of the primary outcome measure.

Treatment groups appeared to be generally matched on relevant measures at baseline.

#### *Primary Efficacy Analyses:*

In the PP population, 20/68 (29.4%) patients in the levobupivacaine group did not achieve pain relief from the first injection, compared with 10/69 (14.5%) patients in the bupivacaine group. The odds ratio was estimated to be 0.40 times higher in the levobupivacaine group compared with the bupivacaine group. The treatment difference was statistically significant with  $p = 0.039$ . In the ITT population, 20/75 (26.7%) patients in the levobupivacaine group did not achieve pain relief from the first injection, compared with 11/84 (13.1%) of bupivacaine patients. The odds ratio was estimated to be 0.37 times higher in the levobupivacaine group compared with the bupivacaine group. The treatment difference was statistically significant with  $p = 0.018$ .

Based on the ITT population (the PP population results were similar), when the patients with no pain relief were excluded from the efficacy analysis, the median duration of pain relief following the first injection was 53 minutes and 58 minutes for levobupivacaine and bupivacaine, respectively. The treatment difference was not statistically significant.

with  $p = 0.16$ . The 90% CI (-14, 2) was within the equivalence limits. However, this result was conditioned upon excluding a significantly larger proportion of patients in the levobupivacaine group compared with the bupivacaine group.

When the patients with no pain relief were included in the analysis, the median duration of pain relief following the first injection was 43 minutes and 53 minutes for levobupivacaine and bupivacaine, respectively. The treatment difference was statistically significant with  $p = 0.005$ . In addition, the 90% CI (-23, -3) resulted in a lower limit that was less than the equivalence limit of 23 minutes specified in the protocol.

#### *Secondary Efficacy Measures:*

The PP population was used in the analyses of the secondary efficacy measures:

#### Duration of Pain Relief Following the First 'Top-up'

There were 60 evaluable patients in the levobupivacaine group and 52 evaluable patients in the bupivacaine group. Six of the levobupivacaine patients and 2 of the bupivacaine patients did not experience pain relief after the first 'top-off.' When the patients not experiencing pain relief were excluded, the mean duration of pain relief was 82 minutes and 76 minutes for levobupivacaine and bupivacaine, respectively. When those patients were included in the analysis, the mean duration of pain relief was 73 minutes and 75 minutes for levobupivacaine and bupivacaine, respectively. The differences were not statistically significant with  $p = 0.62$  for "including patients with no pain relief" and  $p = 0.80$  for 'excluding patients with no pain relief'; and with 90% CI of (-21, 8) and (-15, 12) for the 'inclusion' and 'exclusion' groups, respectively.

#### Time to Onset of Pain Relief:

Both analyses were performed excluding the patients who did not achieve pain relief. The median times to onset of pain relief following the first injection were 12 minutes for both the levobupivacaine and bupivacaine groups. The treatment difference was 0 with 90% CI (-2,2). There was no statistically significant difference in the median time to onset of pain relief following the first injection. The median times to onset of pain relief following the first 'top-up' were 7 minutes for the levobupivacaine group and 6 minutes for the bupivacaine group. The treatment difference was estimated as 1 minute with 90% CI of (0,3).

#### Time Normalized Area Under the VAS Score vs. Time Curve (AUC):

The following rules were used in the calculation of the normalized AUC:

- Where the patient was asleep or had recorded a 'painless' contraction on the verbal rating scale, the missing VAS score was replaced with zero;

- When all VAS scores were missing, no attempt was made to replace them;
- Missing VAS scores at the start of the second stage of labor were ignored;
- If the last score only was missing, it was ignored.

After the first injection, the geometric least squares mean AUC adjusted for imbalance in the baseline VAS value was 22.7 mm in the levobupivacaine group and 15.8 mm in the bupivacaine group. The treatment difference was statistically significant ( $p = 0.018$ ) and the ratio of the means was 1.44 (levobupivacaine/bupivacaine) with the 90% CI of (1.12, 1.85). After the first 'top-up', the geometric least squares mean AUC was 7.3 mm in the levobupivacaine group and 6.6 mm in the bupivacaine group. This difference was not statistically significant and the ratio of the means was 1.09 with 90% CI of (0.82, 1.45). Thus, the levobupivacaine group had a statistically significant greater normalized area under the VAS score vs. time curve following the first injection, but not following the first 'top-up.'

#### Proportion of Patients Recording Each Grade of Motor Block:

Eighty-four percent of the levobupivacaine treated patients had no motor block following the first injection compared with 83% of the bupivacaine patients. The treatment difference was not statistically significant ( $p = 0.90$ ) and the odds ratio was 0.95 with 95% CI of (0.38, 2.33). Following the first 'top-up', 66% of levobupivacaine patients had no motor block compared with 63% of bupivacaine patients. The treatment difference was not statistically significant ( $p = 0.80$ ) and the odds ratio was 0.90 with 95% CI of (0.40, 2.01). Details of recorded grade of motor block for percentages of patients in each of the two groups are summarized in Table 1.3.5 on page 19 of Dr. Tsong's statistical review.

#### Sensory Block:

No formal statistical analysis was performed.

#### Overall Quality of Anesthesia:

No formal statistical analysis was performed. The sponsor provided the following summary statistics: Following the first injection, 51% of the levobupivacaine patients had good analgesia, 26% had fair analgesia, and 15% had poor analgesia, compared with 67% good, 23% fair and 9% poor in the bupivacaine group. Following the first 'top-up', 83% of the levobupivacaine patients had good analgesia vs. 88% in the bupivacaine group.

#### Comments:

A significantly lower proportion of patients achieved pain relief with 0.25% levobupivacaine compared to an equivalent dose of 0.25% bupivacaine. The primary

efficacy outcome was duration of pain relief. Bupivacaine appeared to provide a longer duration of pain relief. The difference was not statistically significant when the patients who did not attain any relief were excluded from the analysis. However, as the larger proportion of these patients were treated with levobupivacaine, when they are included in the analysis there is a statistically significant difference and the lower limit of the 90% CI is outside of the sponsor's predefined equivalence limits.

For the secondary efficacy measures, no significant difference was found between 0.25% levobupivacaine and 0.25% bupivacaine for time to onset of pain relief or for the proportion of patients with motor block. There was a significant difference in the secondary efficacy measure of "time normalized area under the VAS score vs. time curve (AUC)." This result indicates significantly less pain relief was experienced by the patients treated with levobupivacaine compared to those treated with an equivalent dose of bupivacaine.

#### **Study 030433:**

This was a randomized, double-blind, parallel group, single center, up-down, sequential allocation determination of the minimum local anesthetic concentration (MLAC) of levobupivacaine vs. bupivacaine for epidural anesthesia in patients in labor.

Patients were randomized to receive levobupivacaine or bupivacaine in equal proportions. The first patient in each arm received 0.07% study drug. The concentrations studied ranged from 0.05% to 0.11% for the levobupivacaine group and from 0.05% to 0.12% for the bupivacaine group.

The following algorithm was used to determine the concentration to be administered for each patient:

- If the concentration for the previous patient was deemed to be effective, the patient received that dose reduced by 0.01%;
- If the concentration for the previous patient was deemed to be ineffective, the patient received that dose increased by 0.01%;
- If the concentration of study drug given to a previous patient was deemed to be ineffective even with rescue medication, or if the previous patient withdrew from the study, the patient received the same concentration.

Twenty mL of study drug were injected over 5 minutes. Patients recorded their contraction pain using a 100 mm VAS at approximately 15 minute intervals until either 75 minutes after the injection, or until outcome was reached. Recordings were also performed prior to epidural placement and at 15 and 30 minutes post-rescue medication, when administered. Entonox (an equal mixture of nitrous oxide and oxygen) use was also recorded at each time point. Patients were discontinued if the VAS returned to  $\geq 30$  mm.

Four outcomes were defined:

1. Effective: VAS  $\leq$  10 mm during contractions within 30 minutes of the study drug injection and without the use of Entonox;
2. Ineffective: VAS  $>$  10 mm at all times during the 30 minutes following the study drug injection or until rescue medication was administered, whichever occurred first;
3. Reject: VAS  $>$  10 mm at all times during the 30 minutes following the study drug injection and did not respond to rescue medication or a score of  $\leq$  10 mm was recorded but this was associated with the use of Entonox;
4. Withdrawal: patient received non-study drug, failed to reach outcome, refused rescue, withdrew consent, or was otherwise in violation of protocol or a technical failure.

Patients were recruited to replace all "rejects" and "withdrawals." Recruitment continued until there were 30 patients, made up of "effectives" and "ineffectives" in each group.

Using the VAS score for pain of contraction as the primary measure of efficacy, the endpoint was tested to show whether the true difference in MLAC is not greater than a pre-defined 'equivalence limit', specified as  $\pm 0.017\%$ .

Secondary efficacy measures included:

1. Extent of sensory block;
2. Assessment of motor block.

### Results:

Of the 73 patients randomized, all 73 received study medication and were included in the safety analysis. Of these 73 patients, 13 were considered to be protocol violators or "rejects." Thus, 73 patients received study medication, but only 60 were considered eligible for efficacy analysis. There were 7 unevaluable patients in the levobupivacaine group and 6 in the bupivacaine group. Seven patients who were also protocol violators were not withdrawn from the study. Dr. Roberts discusses these patients on page 90 of her review. The choice to maintain these seven patients in the study appears to have been appropriate.

Treatment groups appeared to be generally matched on relevant measures at baseline.

### *Primary Efficacy Analyses:*

The MLAC median values were 0.083% and 0.081% for levobupivacaine and bupivacaine, respectively. The difference was 0.002 with 95% CI of (-0.031, 0.035). This failed to lie within the predefined equivalence limits. These results indicate an analysis which failed to establish dose potency equivalence between levobupivacaine and

bupivacaine. Based on the CI, however, one cannot rule out a 42% reduction or 38% increase in potency.

*Secondary Efficacy Measures:*

Secondary efficacy measures were not statistically analyzed. However, the sponsor did provide descriptive statistics which Dr. Roberts has summarized on pages 98 of her review.

**Comments:**

This study attempted to demonstrate equivalent potency for levobupivacaine and bupivacaine with a complicated dosing algorithm. The results indicate that the estimated concentrations required to achieve pain relief were approximately the same. However, equivalence was not established based upon the sponsor's predefined equivalence range.

**CENTRAL BLOCK STUDIES:**

**STUDY 006175:**

This was a randomized, double-blind, parallel group, multicenter study comparing 0.5% levobupivacaine, 0.75% levobupivacaine and 0.5% bupivacaine for epidural anesthesia in patients undergoing elective lower limb vascular surgery or arthroscopy.

Patients were randomized to one of the three treatment arms, either 0.5% levobupivacaine, 0.75% levobupivacaine or 0.5% bupivacaine via epidural catheter, just prior to elective surgery. A total of fifteen milliliters of study drug was infused. Patients were pretreated with temazepam 20 mg, and propofol and fentanyl were used on an as needed basis.

The primary measure of efficacy was the duration of block. Duration of block was defined in the protocol as the time from first analgesia to pinprick to time of return of sensation in all dermatomes. For patients who required general anesthesia for inadequate block, the time of this intervention was used instead of the time of return of sensation. However, the sponsor changed this definition, after the blind had been broken, to: time to onset of sensory/motor block until complete return of sensation/function irrespective of whether or not a general anesthetic was given. Patients who did not achieve a block were excluded from the analyses.

Secondary efficacy measures included:

1. Time to onset of sensory block;
2. Time to onset of and duration of motor block;

### 3. Overall assessment of quality of block.

The sponsor also analyzed the following secondary efficacy measures defined after the blind had been broken:

1. Maximum height, and time to maximum height, of sensory block;
2. Time to onset and duration of block at selected dermatomes;
3. Time to onset and duration of each grade of motor block;
4. Proportion of patients responding at each grade of motor block.

#### **Results:**

Of the 96 patients randomized, 88 received study medication and were included in the safety analysis. No further withdrawals occurred, and these 88 patients comprised the ITT population. Seven patients were excluded from the Per-Protocol [PP] population (2 from the levobupivacaine 0.5% group, 4 from the levobupivacaine 0.75% group, and 1 from the 0.5% bupivacaine group) due to having received prohibited medication during the procedure. An additional 4 patients were "partially" excluded from the efficacy analyses. Three of these patients received a general anesthetic before onset of block on both sides. These patients were excluded from all analyses on the unblocked side, but were included in the overall assessment of block. The fourth patient had a unilateral block and was excluded from the analyses by the sponsor after the blind had been broken.

Treatment groups appeared to be generally matched on relevant measures at baseline.

#### *Primary Efficacy Analyses:*

The following table summarizes the numbers and percentages of patients who did not attain a sensory block on their right or left side.

**Table 2.**

Study Drug Dose	Right Side N (%)	Left Side N (%)
Levobupivacaine 0.5%	2 (7)	4 (14)
Levobupivacaine 0.75%	1 (3)	2 (7)
Bupivacaine 0.5%	2 (7)	1 (3)

There were no significant differences in mean duration in either left or right sided sensory blocks among the three treatment groups, using the ITT population. When the analysis

was performed using the sponsor's revised duration time criteria, the 0.75% levobupivacaine group had a significantly longer duration of block compared to the other two groups. This treatment effect was statistically significant for both left ( $p = 0.008$ ) and right ( $p = 0.002$ ) sided sensory blocks. The PP population analysis resulted in similar outcomes.

#### *Secondary Efficacy Measures:*

All secondary efficacy results are based on analyses performed on the PP population, unless stated otherwise.

#### Time to Onset of Sensory Block:

There were no statistically significant differences in time to onset of sensory block for either the right or left side for the three treatment arms ( $p = 0.22$  for the left side and 0.26 for the right side, for the ITT population). The results for the PP population are similar. The results for both populations are summarized in Dr. Tsong's Table 11.1.2, page 28 of his review.

#### Time to Onset of and Duration of Motor Block:

Although a lower percentage of patients treated with 0.5% levobupivacaine (52% left side; 45% right side) attained motor block compared with patients treated with 0.75% levobupivacaine (77% left side; 73% right side) or 0.5% bupivacaine (66% left side; 69% right side), these differences were not statistically significant. There were no statistically significant differences in the mean duration or time to onset for right sided motor blocks among the three groups. The 0.75% levobupivacaine group did have a statistically significantly longer duration of motor block on the left compared to 0.5% levobupivacaine ( $p = 0.014$ ). There were no statistically significant differences in mean duration between either levobupivacaine group and the bupivacaine group.

#### Overall Quality of Block:

The percentage of failure was analyzed and there were no statistically significant differences among the three groups. The results of this measure are summarized in Dr. Tsong's Table 11.1.3, page 28 of his review.

#### Maximum Height, and Time to Maximum Height, of Sensory Block:

There was no evidence of a statistically significant difference among the three groups in either maximum height of block or time to maximum height using the ITT population.

#### Time to Onset and Duration of Block at Selected Dermatomes:

There was no evidence of a statistically significant difference among the three groups in

time to onset at any of the dermatomes considered (S5, S3, S1, L5, L2, T12, T8, T6 and T4). There was a significantly longer duration of sensory block at S3, S1 and L5, on average, for the levobupivacaine 0.75% group compared to the 0.5% bupivacaine.

#### Time to Onset and Duration of Each Grade of Motor Block:

There was no evidence of a statistically significant difference among the three groups in either time to onset or duration of block for the lower grade blocks. Only 2 patients achieved a motor grade 3 block and their data was not analyzed.

#### Proportion of Patients Responding at Each Grade of Motor Block:

There was no evidence of a significant difference in response rates between the three groups for each grade of motor block.

#### Comments:

Although the duration of sensory block was statistically significantly longer for 0.75% levobupivacaine compared to 0.5% bupivacaine or 0.5% levobupivacaine, this result was based on an analysis amended by the sponsor after the study blind had been broken. The original analysis did not show a statistically significant difference. There were no statistically significant differences in time to onset of sensory block, or duration or time to onset of motor block, between the three groups.

#### STUDY CS-005:

This was a randomized, double-blind, parallel group, single center study comparing 0.75% levobupivacaine and 0.75% bupivacaine for epidural anesthesia in patients undergoing scheduled major abdominal surgery.

Patients were randomized 1:1 to either 0.75% levobupivacaine or 0.75% bupivacaine via epidural catheter. Twenty milliliters of study drug was infused over 5 minutes. During surgery patients received another 7 mL of study drug as needed. Patients were pretreated with midazolam 1 to 5 mg, antibiotics and cimetidine. Propofol and additional doses of midazolam were permitted during the procedure as needed.

The primary measure of efficacy was the time to onset of sensory block adequate for surgery. This was defined as analgesia at T10, bilaterally.

Secondary efficacy measures included:

1. Time to T10 regression;
2. Time to complete regression;
3. Abdominal wall relaxation (using the RAM score);
4. Patient pain rating at each of three time points;

5. Time to onset and offset of motor block;
6. Maximum upper level;
7. Time to maximum upper level;
8. Time to two-level regression;
9. Duration of sensory and motor blocks;
10. Muscle relaxation;
11. Overall assessment.

### **Results:**

Of the 57 patients randomized, 56 received study medication and were included in the safety analysis. No further withdrawals occurred, and these 56 patients comprised the ITT population. One patient in the bupivacaine group did not achieve the specified block and was not included in the PP population.

Treatment groups appeared to be generally matched on relevant measures at baseline.

### ***Primary Efficacy Analyses:***

In the ITT population, the mean time to onset of sensory block was 13.6 minutes and 14.0 minutes for the levobupivacaine and bupivacaine groups, respectively. The treatment difference of -0.4 minutes was not statistically significant ( $p = 0.782$ ) with 95% CI of (-4.71, 3.91). This was within the equivalence limits of -7.58 and 7.58 chosen by the sponsor in the protocol. Similar results were found when the PP population was analyzed.

### ***Secondary Efficacy Measures:***

All secondary efficacy results are based on analyses performed on the ITT population unless otherwise noted.

### **Time to T10 Regression:**

The mean times to T10 regression of sensory block were 375.0 minutes and 340.1 minutes for the levobupivacaine and bupivacaine groups, respectively. The treatment difference was estimated as 35.0 minutes with 95% CI of (-14.6, 84.6). The difference was not statistically significant with  $p = 0.216$ .

### **Time to Complete Regression:**

The mean value of the time to complete regression was 550.6 minutes and 505.9 minutes for levobupivacaine and bupivacaine, respectively. The treatment difference was estimated as 44.6 minutes with 95% CI of (1.9, 87.4). The difference was statistically significant with  $p = 0.016$ .

### Abdominal Wall Relaxation:

Using the RAM (rectus abdominis muscle) score, a six point scale from "0 = able to rise to sitting position with hands behind head" to "5 = no muscle tension or movement", the 30 minute presurgical assessment of abdominal wall relaxation resulted in a mean difference of 0.4 points favoring levobupivacaine (mean = 3.4) over bupivacaine (mean = 3.8). The 95% CI was (-0.9, 0.0). There were no statistically significant differences between the two groups on any presurgical RAM scores.

### Patient Pain Rating:

Patients used a 4 point scale (0 = none, 3 = severe) during surgery, at the conclusion of surgery, and prior to leaving the recovery room. Levobupivacaine treated patients had less pain (mean = 0.2) at the conclusion of surgery compared to bupivacaine (mean = 0.6). The treatment difference was estimated to be -0.4 with 95% CI of (-0.8, 0.0). The difference was not statistically significant ( $p = 0.072$ ). No statistically significant differences were found at any of the time points.

### Time to Onset and Offset of Motor Block:

Four (14%) patients in the levobupivacaine group and 20 (71%) patients in the bupivacaine group experienced motor block prior to surgery. This difference was statistically significant ( $p < 0.001$ ).

The mean duration of motor block (the sponsor chose to define duration of motor block as the time from Time 0 to Offset of Motor Block) was 355.4 minutes for levobupivacaine and 375.7 minutes for bupivacaine. The difference was estimated as -20.3 minutes with 95% CI of (-70.9, 30.4). The difference was not statistically significant with  $p = 0.311$ .

### Maximum Upper Level:

The mean maximum level bilaterally was between T5 and T6 for both groups. The difference between the treatment groups was 0.3 dermatomes with 95% CI of (-1.7, 1.2). The treatment difference was not statistically significant with  $p = 0.729$ .

### Time to Maximum Upper Level:

The mean time to maximum upper level bilaterally was 24.3 and 26.5 minutes for the levobupivacaine and bupivacaine groups, respectively. The treatment difference was estimated to be -2.2 minutes with 95% CI of (-8.3, 4.0). This difference was not statistically significant with  $p = 0.642$ .

### Time to Two-level Regression:

The mean time to two-level regression of sensory block bilaterally was 300.8 minutes for the levobupivacaine group and 292.7 minutes for the bupivacaine group. The treatment difference was estimated to be 8.1 minutes with 95% CI of (-40.6, 56.9). The difference was not statistically significant with  $p = 0.917$ .

### Duration of Sensory and Motor Blocks:

The mean duration of sensory block was 361.6 minutes for levobupivacaine and 327.7 minutes for bupivacaine. The treatment difference was estimated as 33.8 minutes with 95% CI of (-16.5, 84.1). The difference was not statistically significant with  $p = 0.183$ .

The mean duration of motor block was 355.4 minutes for levobupivacaine and 375.7 minutes for bupivacaine. The difference was estimated as -20.3 minutes with 95% CI of (-70.9, 30.4). The difference was not statistically significant with  $p = 0.311$ . This analysis was performed with exclusion of patients who did not experience motor block. This may have biased the results toward not finding a difference.

### Muscle Relaxation:

Using a four point scale (from 0 = poor to 3 = excellent), muscle relaxation was assessed by the anesthesiologists and by the surgeons. The anesthesiologists' mean score was 2.3 minutes for the levobupivacaine group and 2.2 for the bupivacaine group. The treatment difference was estimated to be -0.1 with 95% CI of (-0.3, 0.6). The difference was not statistically significant with  $p = 0.505$ .

The surgeons' mean score was 2.3 minutes for the levobupivacaine group and 2.0 for the bupivacaine group. The treatment difference was estimated to be 0.4 with 95% CI of (0.0, 0.8). The difference was not statistically significant with  $p = 0.074$ .

### Overall Assessment:

No analysis of this outcome measure was reported by the sponsor.

### Comments:

For the primary efficacy outcome, 0.75% levobupivacaine and 0.75% bupivacaine had mean times to onset of sensory block that met the sponsor's predefined equivalence margin. However, this margin of 8 minutes is of questionable clinical value.

A statistically significantly longer time to complete regression of sensory block was found for levobupivacaine compared to bupivacaine. Dr. Roberts comments that this "...45 minute difference between levobupivacaine and bupivacaine with respect to time to complete regression of block is of specific relevance." [page 137 of her review]

There were no statistically significant differences between the treatment groups for muscle relaxation, pain control, or time to onset and duration of sensory and motor block.

## **CENTRAL BLOCK PAIN MANAGEMENT STUDIES:**

### **STUDY 030475:**

This was a randomized, double-blind, parallel group, multicenter study comparing three doses of bupivacaine (0.0625%, 0.125% and 0.25%) administered as a continuous epidural infusion for post-operative pain in patients undergoing elective orthopedic surgery.

Patients were randomized to one of the three treatment arms, either 0.0625% levobupivacaine, 0.125% levobupivacaine or 0.25% levobupivacaine. Ten milliliters of study drug was administered prior to surgery. The first 3 mL were injected as a test dose, followed by the remaining 7 mL. Further 5 mL injections were given as needed to maintain an adequate sensory level for surgery. Patients were pretreated with temazepam 20 mg and ranitidine 150 mg. Thirty minutes after the last bolus injection, an infusion of one of the above three concentrations was administered at a rate of 6 mL/hr and continued for 24 hours.

The primary measure of efficacy was the time to the first request for analgesia during the 24 hour infusion period. At the initial request for rescue analgesia, patients received 2 mg doses of IV morphine until acceptable pain control was achieved. A PCA pump was then activated and patients were allowed to titrate the morphine themselves. Patients recorded their pain hourly until 4 hours following the start of the epidural infusion; then every 2 hours for the next 8 hours, followed by every 6 hours up to 24 hours.

Secondary efficacy measures included:

1. Normalized Dose of Morphine Administered;
2. Normalized Number of Requests for Morphine via PCA Pump;
3. Visual Analogue Pain Scores [VAS];
4. Height of Sensory Block;
5. Motor Block.

### **Results:**

One hundred and five patients were randomized. The following table [copied from Dr. Robert's Table 80, page 148 of her review] summarizes the disposition of these 105 patients:

Table 3.

Patients	0.0625% L-bupivacaine N (%)	0.125% L-bupivacaine N (%)	0.25% L-bupivacaine N (%)	Total N (%)
Randomized	36 (34.3%)	33 (31.4%)	36 (34.3%)	105
Excluded from Safety Population	2	4	1	7
Safety Evaluable	34 ( 94.4% )	29 ( 87.8% )	35 ( 97.2 % )	98 (93.3 % )
Excluded from ITT Population	2	2	3	7
Intent-to-Treat Population	32 ( 94.1% )	27 ( 93.1% )	32 ( 91.4% )	91 ( 86.7% )
Excluded from Per- Protocol	4	6	5	15
Per-Protocol Population	28 ( 87.5% )	21 ( 78% )	27 ( 84.3 % )	76 ( 72.3 % )

The predominant reason for patients being excluded from the ITT group was "insufficient block." However, one patient was not included in the ITT group because of an adverse event. That adverse event was reported as severe bradycardia (< 30 bpm) with transient severe decreased cardiac output. Patients were excluded from the PP group for time window violations or for having received prohibited medications.

Treatment groups appeared to be generally matched on relevant measures at baseline.

*Primary Efficacy Analyses:*

Fifteen patients (46.9%) in the 0.25% group, 3 patients (11.9%) in the 0.125% group, and 1 patient (3.1%) in the 0.0625% group, did not require any relief analgesia. After adjustment for multiple comparisons, the following results were noted:

1) The difference in proportions was statistically significant ( $p = 0.001$ ) with the relative risk of requesting analgesia being: 0.548 for 0.25% vs. 0.125%, with 95% CI of (0.409, 0.736); and, 0.598 for 0.25% vs. 0.0625%, with 95% CI of (0.421, 0.842). There was no statistically significant difference between the 0.125% and 0.0625% treatment groups.

2) The mean time to first request for analgesia was 16.664 hours for the 0.25% treatment group, 9.506 hours for the 0.125% treatment group, and 8.106 hours for the 0.0625% treatment group. The treatment difference (estimated at -6.888 hrs) for the 0.25% vs. 0.125% groups was statistically significant with  $p < 0.001$  with 95% CI of (-10.521, -3.255). The treatment difference (estimated at -8.120 hrs) for the 0.25% vs. 0.0625% groups was also statistically significant with  $p < 0.001$  with 95% CI of (-11.587, -4.652).

The treatment difference (estimated at -1.231 hrs) between the 0.125% and the 0.0625% groups was not significantly different with  $p = 0.49$  with 95% CI of (-4.828, 2.365).

3) A secondary analysis was performed using survival analysis. The 0.25% group had a hazard rate ratio of 1.791 to 0.125% which was statistically significantly greater than one ( $p < 0.001$ ). The ratio of the 0.25% group to the 0.0625% group was 4.181, which was also statistically significantly greater one ( $p < 0.001$ ). The survival curves of the 0.125% and 0.0625% groups were similar and the treatment difference was not statistically significant ( $p = 0.19$ ) adjusted for center, and ( $p = 0.80$ ) adjusted for type of surgery. Analysis using the PP population gave similar results. The results of this analysis confirm the results of the first analysis.

#### *Secondary Efficacy Measures:*

Adjustments to the statistical analyses were made in order to account for multiple comparisons.

#### Normalized Dose of Morphine Administered:

For the ITT population, the median normalized dose of morphine administered was 0.21 mg for the 0.25% group, 0.96 mg for the 0.125% group, and 1.50 mg for the 0.625% group. The treatment differences between 0.25% and 0.125%, and between 0.25% and 0.0625%, were statistically significant, with  $p = 0.003$  for the first comparison and  $p < 0.001$  for the second comparison. The treatment difference between the 0.125% and the 0.0625% groups was not statistically significant with  $p = 0.16$ .

#### Normalized Number of Requests for Morphine:

For the ITT population, the median number of requests for morphine was 0/hr for the 0.25% group, 1.48/hr for the 0.125% group, and 1.46/hr for the 0.625% group. The treatment differences between 0.25% and 0.125%, and between 0.25% and 0.0625%, were statistically significant, with  $p < 0.001$  for both comparisons. The treatment difference between the 0.125% and the 0.0625% groups was not statistically significant with  $p = 0.72$ .

#### Visual Analogue Pain Scores:

No formal statistical analyses were performed on this data. Descriptive statistics reveal a trend for the 0.25% group to have the lowest mean VAS scores and the 0.0625% group to have the highest mean VAS scores.

#### Height of Sensory Block:

There were small variations between the treatment groups, but no formal statistical analyses were performed on this data.

### Motor Block:

The 0.125% group had a higher odds ratio (3.972) for higher grade of motor block than the 0.0625% group. The odds ratio was statistically significantly larger than 1 ( $p = 0.012$ ). The 95% CI was estimated to be (1.356, 11.637). The odds ratio for the 0.25% group to the 0.0625% group was estimated to be 8.004. It was significantly larger than 1 ( $p < 0.001$ ) with an estimated 95% CI of (2.750, 23.291). The odds ratio for the 0.25% group to the 0.125% group was estimated to be 1.289 and was not statistically significant ( $p = 0.30$ ). The 95% CI was (0.799, 2.080).

### Comments:

The primary analyses reveal a statistically significant increase in time to first request for analgesia for 0.25% levobupivacaine compared to either 0.125% levobupivacaine or 0.0625% levobupivacaine. The treatment effect was not statistically significantly different for 0.125% and 0.0625% levobupivacaine. Consistent results were seen in the secondary analyses of "dose of morphine administered" and "number of requests for morphine."

Treatment with the 0.25% dose of levobupivacaine resulted in a statistically significantly higher odds ratio of patients developing a higher grade of motor block compared to patients treated with either 0.125% or 0.0625% levobupivacaine.

### STUDY CS-004:

This was a randomized, double-blind, parallel group, multicenter study comparing 0.25% levobupivacaine, 0.25% levobupivacaine with 0.005% morphine, and 0.005% morphine administered as a continuous epidural infusion for post-operative pain in patients undergoing major abdominal surgery.

Patients were randomized 1:1:1 to one of the three treatment arms: either 0.25% levobupivacaine, 0.25% levobupivacaine with 0.005% morphine, or 0.005% morphine. The patients were pretreated with midazolam 0.5 to 4.0 mg. Prior to surgery, patients were administered 6 to 12 mL of 0.75% levobupivacaine via an epidural catheter, following a test dose of 3 mL of 1.5% lidocaine with 15 micrograms of epinephrine. An additional 5 mL of 0.75% levobupivacaine was administered after 15 minutes as necessary. Patients who had inadequate sensory block at 45 minutes were withdrawn from the study and treated with alternate anesthesia. General anesthesia was induced with propofol or etomidate, and maintained with sevoflurane or isoflurane. Neuromuscular blocking agents were used at the discretion of the investigator.

At the end of surgery, patients received a 2 mL bolus of blinded study medication, which consisted of either 0.1% morphine for the two groups randomized to receive morphine, or saline for the group randomized to receive study medication. Patients were then

administered study drug infusion and maintained on those infusions for 24 hours. If the infusion failed to provide adequate analgesia, the patient received additional medication according to the following regimen:

- a. A loading dose of 4 mL of study medication was given and the infusion was increased by 2 mL to 6 mL/hr.
- b. If analgesia remained inadequate after one hour, an additional 6 mL of study medication was administered and the infusion rate was increased by another 2 mL/hr to 8 mL/hr.
- c. If after one additional hour the patient was still experiencing pain, an additional loading dose of 8 mL was administered and the infusion rate was again increased by 2 mL/hr to 10 mL/hr.

Ketorolac was administered as supplemental analgesia as needed at any time after the initial loading dose and increase in infusion rate of study drug. Patients were allowed to receive up to 30 mg every 6 hours (for those under 60 years of age) or 15 mg every 6 hours (for those over 60 years of age).

The primary measure of efficacy was the time to the first request for analgesia during the 24 hour infusion period. The key comparison was between the combination treatment group and the morphine only treatment group.

Secondary efficacy measures included:

1. Proportion of patients who did or did not request rescue analgesia;
2. Amount of rescue medication administered;
3. Rate of administration of rescue medication;
4. Proportion of patients who requested ketorolac and the amount of ketorolac administered;
5. Extent of motor block
6. Patient VAS at rest and when coughing;
7. Global VAS by patient and investigator.

## Results:

A total of 68 patients were randomized at two sites. Of the 68 patients, 66 received study medication and were included in the safety population. Two levobupivacaine treated patients were excluded from the ITT population because adequate block had not been achieved at 15 minutes after additional injection. Four patients (two levobupivacaine treated and two morphine treated) were excluded from the PP population because they received protocol prohibited narcotics intraoperatively. Twenty-four patients discontinued before the end of the study but were included in the PP population. The following table copied from Dr. Roberts' Table 98, page 180 of her review, summarizes the patient disposition:

Table 4.

Table 3 Patient Disposition

Patients	Levobupivacaine/ Morphine N (%)	Levobupivacaine N (%)	Morphine N (%)	All Patients N (%)
Randomized	22 (100)	23 (100)	23 (100)	68 (100)
Safety Population	21 (95.5)	22 (95.7)	23 (100)	66 (97.1)
ITT Population	21 (95.5)	21 (91.3)	22 (95.7)	64 (94.1)
Per-Protocol Evaluable	21 (95.5)	19 (82.6)	20 (87.0)	60 (88.2)
Total Discontinued	2 (9.1)	13 (56.5)	9 (39.1)	24 (35.3)
Total Completed	20 (90.9)	10 (43.5)	14 (60.9)	44 (64.7)

Abstracted from Statistical Table 1

Treatment groups appeared to be generally matched on relevant measures at baseline.

#### Primary Efficacy Analyses:

The following table copied from Dr. Roberts' Table 100, page 182 of her review, summarizes the results for the primary outcome variables:

Table 5.

Table 6 Time (Minutes) to First Request for Rescue Analgesia

Time to first request for rescue (min)	Levobupivacaine/ Morphine	Levobupivacaine	Morphine
Percentile			
25%	353.0	60.0	86.0
50%	>144.0*	174.0	480.5
75%	>144.0	255.0	>144.0
Number of censored observations <sup>a</sup>	11	1	6
Mean <sup>1,2</sup>	16.04	4.26	10.94

\*Censored at 24 hours (patients who never requested rescue medication). <sup>1</sup>Arithmetic Mean. <sup>2</sup>If rescue analgesia was not requested during the 24-hour study period, the time of the first request of rescue medication was censored at the completion time of the study drug in the 24-hour post-operative period. Means calculated using censored data are negatively biased. Due to differential group censoring, the combination group has the greatest negative bias and the levobupivacaine treatment has the least negative bias.

Pairwise Comparisons:	p-value
Combination versus Morphine	0.066
Levobupivacaine versus Morphine	0.001
Combination versus Levobupivacaine	0.001

Abstracted from Statistical Table 7.1.

Adjustments to the statistical analyses were made in order to account for multiple comparisons. There were 10/21 patients in the combination treatment group, 16/22 in the morphine only group, and 20/21 in the levobupivacaine only group who requested rescue medication. The relative risk of requesting rescue medication for the combination treatment group compared to the morphine only group was 0.66 which was not statistically significantly different from 1 ( $p = 0.062$ ). The sample mean of the three treatment groups were: 962.4 minutes for the combination treatment, 255.6 minutes for the levobupivacaine only treatment, and 656.4 minutes for the morphine only group. The treatment difference between the combination treatment group and the morphine only group was not statistically significant with  $p = 0.066$ . However, patients who did not request any rescue medication were considered censored data, and the moderately unequal censoring which occurred may have negatively biased the results of this analysis. Similar results were noted when the PP group is analyzed.

The relative risk of requesting rescue medication for the combination group compared to the levobupivacaine only group was 0.50 which was statistically significantly different from 1 ( $p = 0.001$ ). The relative risk of requesting rescue medication for the levobupivacaine only group compared to the morphine only group was 1.31 which was not statistically significantly different from 1 ( $p = 0.044$ ; note that adjustment for multiple comparisons required a p-value of 0.017). In the survival analysis the levobupivacaine only group had a statistically significantly shorter time to the first request for rescue medication than the combination treatment group ( $p = 0.001$ ) or the morphine only group ( $p = 0.001$ ).

#### *Secondary Efficacy Measures:*

##### Proportion of Patients Who Did or Did Not Request Rescue Analgesia:

This outcome measure is discussed above in relation to the primary efficacy analysis.

##### Amount of Rescue Medication Administered:

The adjusted mean volume of rescue medication was 115.28 mL for the combined group, 122.11 mL for the levobupivacaine only group, and 103.42 mL for the morphine alone group. The differences were estimated to be: -6.83 mL with 95% CI of (-36.26, 22.61) for the combination vs. levobupivacaine, 11.86 mL with 95% CI of (-17.22, 40.95) for the combination vs. morphine, and 18.69 mL with 95% CI of (-10.62, 47.64). None of these differences were statistically significant with  $p = 0.644$ , 0.418 and 0.201.

##### Rate of Administration of Rescue Medication:

The rate of administration of rescue medication was lower in the combination group

(adjusted mean 5.0 mL/hr) than in the morphine group (5.9 mL/hr). The difference was not statistically significant ( $p = 0.109$ ).

#### Proportion of Patients Who Requested Ketorolac and the Amount of Ketorolac Administered:

The difference in the proportion of patients requesting Ketorolac between the combination group and the morphine only group (7/21 for the combined group, 14/22 for the morphine only group, and 18/21 for the levobupivacaine only group) was statistically significant ( $p = 0.040$ ). However, for those who did request the medication, the amount did not differ significantly across the treatment groups.

#### Extent of Motor Block:

There was no evidence of a difference in duration of motor block between the combination and morphine only groups. Post-surgery block was assessed every 4 hours for 24 hours. At the 4 hour point, approximately 80% of all study patients had a score of 0 (no paralysis). At eight hours, all patients had full movement of their legs.

#### Patient VAS at Rest and When Coughing:

VAS scores were obtained every 4 hours post-surgery. At rest, the combination group had a statistically significantly lower score than the morphine only group ( $p = 0.001$ ) at 8 hours, but not at 20 or 24 hours ( $p = 0.081$  and  $0.101$ , respectively). While coughing, the combination group had a lower VAS score than the morphine only group at 4 hours and 8 hours ( $p < 0.05$ ). However, after adjusting for multiple comparisons, the difference was no longer statistically significant.

#### Global VAS by Patient and Investigator:

Patients in the combination group had the lowest overall assessment of pain at 2.35, compared to the morphine only group at 3.56 and the levobupivacaine only group at 4.43. The treatment difference for the combination group vs. the morphine only group was not statistically significant ( $p = 0.167$ ). The difference for the combination group and the levobupivacaine only group was statistically significant ( $p = 0.029$ ). Similar results occurred with the investigators' overall assessment of pain. The treatment difference for the combination vs. morphine only groups was marginally significant ( $p = 0.056$ ), and the difference for the combination group and the levobupivacaine only group was statistically significant ( $p < 0.001$ ).

#### **Comments:**

Although the treatment difference between the combination treatment group and the morphine only treatment group for the primary outcome measure of "time to first request for rescue medication" was not statistically significant, the trend was in the direction of

greater pain control for the combination treatment, compared to either of the other two treatments. The relative risk for requesting rescue medication was smaller for the combination group compared to the morphine only group, but not statistically significant. The relative risk was smaller for the combination treatment group compared to the levobupivacaine only group and was statistically significant. Also, the survival analysis showed that the levobupivacaine treated patients had a statistically significantly shorter time to requesting rescue medication compared to either the morphine only or combination treatment patients.

There were no statistically significant differences between the groups for amount or rate of administration of rescue medication. The greatest number of requests for ketorolac were made by levobupivacaine only treatment patients. The least number of requests were made by combination treatment patients. However, for the patients who did request the drug, the actual amount of ketorolac taken did not differ across the groups. No differences were seen between the groups for extent of motor block. The results for pain relief were variable, although there did appear to be a trend for the combination treatment to be superior to morphine alone, which appeared to be superior to levobupivacaine alone.

#### **STUDY CS-006:**

This was a randomized, double-blind, parallel group, multicenter study comparing 0.125% levobupivacaine, 0.125% levobupivacaine with fentanyl, and fentanyl alone, administered as a continuous epidural infusion for post-operative pain in patients undergoing major orthopedic surgery.

Patients were randomized 1:1:1 to one of the three treatment arms: either 0.125% levobupivacaine, 0.125% levobupivacaine with 4 mcg/mL fentanyl, or 4 mcg/mL fentanyl. The patients were pretreated with midazolam 0.5 to 4.0 mg. Prior to surgery, patients were administered 0.75% levobupivacaine via an epidural catheter to a maximum of 20 mL, including a test dose of 3 mL of 0.75% levobupivacaine with 15 micrograms of epinephrine. An additional 5 mL of 0.75% levobupivacaine was administered after 15 minutes as necessary. Immediately following this bolus injection, patients were started on study drug infused at 4 mL/hr. Propofol and additional doses of midazolam were administered intraoperatively as needed.

After leaving the operating room, patients self-administered study drug via patient controlled epidural anesthesia [PCEA] for a period of 24 hours. If the infusion failed to provide adequate analgesia, the patient could self-administer 2 mL every 10 minutes to a maximum of 14 mL/hr. If analgesia remained inadequate, the patient was administered a loading dose of 5 mL of study drug and the infusion rate was increased to 6 mL/hr. If after 30 minutes the patient still complained of pain, another 5 mL loading dose was administered and the infusion rate was increased to 8 mL/hr. If the patient continued to complain of pain a femoral block was considered. If the block was performed, the patient was discontinued from the study at that point.

The primary measure of efficacy was the time to the first request for PCEA during the 24 hour infusion period. The key comparison was between the combination treatment group and the fentanyl only group.

Secondary efficacy measures included:

1. Proportion of patients who requested rescue analgesia;
2. Amount of rescue medication administered;
3. Proportion of patients who required femoral nerve block;
4. Extent of motor block;
5. Pain (VAS) assessment;
6. Overall pain assessment at end of 24 hours.

### Results:

A total of 68 patients were randomized at two sites. Of the 68 patients, 66 received study medication and were included in the safety population. One patient (randomized to the combination treatment group) was excluded from the ITT population after receiving 0.75% levobupivacaine as presurgical anesthesia and experiencing an intravascular injection. Four patients (one levobupivacaine treated and three combination treated) were excluded from the PP population because of technical failure. One levobupivacaine treated patient was excluded from the PP population based on 'protocol violation.' Twenty-eight patients discontinued before the end of the study but were included in the PP population. The following table copied from Dr. Roberts' Table 106, page 198 of her review, summarizes the patient disposition:

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ON ORIGINAL